A Family of New 1,2,4-Trioxanes by Photooxygenation of Allylic Alcohols in Sensitizer-Doped Polymers and Secondary Reactions

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Dedicated to Professor Bernd Giese on the occasion of his 65th birthday

Abstract: Type II photooxygenation (singlet oxygen) is described as a synthetically useful way for the preparation of allylic hydroperoxides and endoperoxides using sensitizer-adsorbed or covalently sensitizer-doped polymeric (macro- or nanosized) containers. Facilitated product separation and purification as well as increased reactivity are advantages of these techniques in comparison with solution-phase photochemistry. The products generated by Type II photooxygenation have been used for the syntheses of numerous polycyclic peroxides with a common 1,2,4-trioxane core as exhibited in the natural antimalarial artemisinin.

Key words: photochemistry, catalytic oxygenation, peroxides, peroxyacetals, Lewis acid catalysis

Introduction

Photooxygenation processes are classified as Type I, II, and sometimes also as Type III.[2] These codifications stand for radical-induced oxygenation (with triplet oxygen as the transfer reagent), energy-transfer oxygenation (with singlet excited oxygen as the reagent), and for electron-transfer oxygenation (with triplet oxygen or with the superoxide anion radical as reagent). Especially the Type II photooxygenation has been used for numerous synthetic applications because singlet oxygen ($^1\Delta_g$) is a highly reactive and at the same time selective reagent showing remarkable chemo-, regio-, and stereoselectivity patterns.[3] Recently, even the first enantioselective singlet oxygen reactions under organocatalytic conditions were reported.[4] The conventional reaction conditions nicely correspond to the principles of sustainable 'green' chemistry,[5] i.e. triplet oxygen from air is the reagent and the energy-transfer sensitizers can be as simple as natural porphyrins or xanthene dyes.

Beside these attractive features, however, singlet oxygen has unfavorable properties under environmentally clean conditions, e.g. in aqueous media. The lifetime of the $^1\Delta_g$ state, an essential parameter for reactions with electronically excited species, is in the microsecond region in protic solvents and rises to milliseconds only in chlorinated or fluorinated solvents.[6]

In recent publications we have described a relatively simple approach to improved reaction conditions: the use of polymeric micro- or nanosized containers with the porphyrin sensitizer incorporated either adsorbed in the polymer network or covalently linked during the polymerization process.[7] A favorable dye for the adsorptive approach was tetrakis-4-methylphenylporphyrin (TTP); for the covalently linked polymers, either tetrakis-4-vinylphenylporphyrin (TSP) or protoporphyrin IX (PP-IX) were used (Figure 1).[8] The nanosized polymer beads

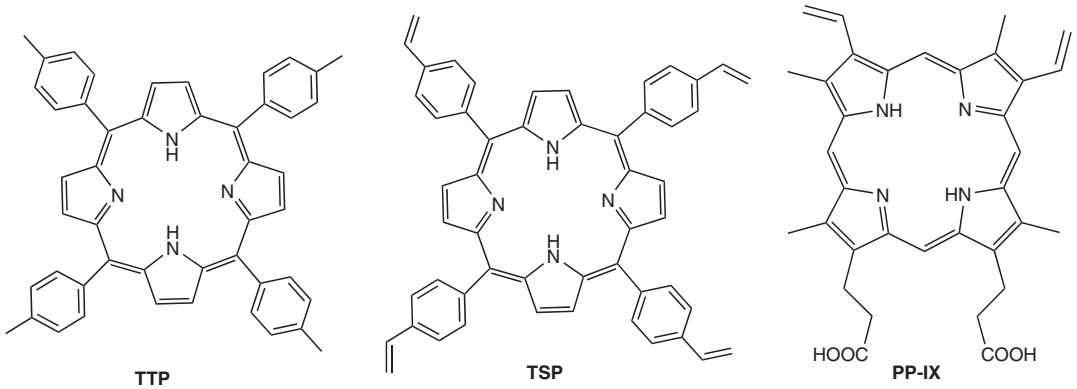

Figure 1 Monomeric dyes for adsorption and linking to polymers.

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Biographical Sketches

from left to right: A. Bartoschek, T. T. El-Idreesy, A. G. Griesbeck, L.-O. Höinck, J. Lex, C. Miara, J. Neudörfl

Anna Bartoschek was born in Tychy, Poland, in 1974. She studied chemistry and mathematics at the University of Cologne from 1994 and received her first state examination in 2001. She is currently finishing her doctoral thesis on the use of polymer supports for photooxygenation reactions under the supervision of Prof. A. Griesbeck.

Tamer T. El-Idreesy was born in Cairo, Egypt, in 1975. He studied chemistry at the University of Cairo from 1992 and received his B.Sc. in 1996. In 2000 he came to Germany with a Ph.D. long-term scholarship from the Egyptian government. He carried out his doctoral thesis on the synthesis of novel peroxide compounds under the supervision of Prof. Axel G. Griesbeck and received his doctoral degree in 2005. He is recipient of the Kurt–Alder award of the University of Cologne for the best thesis in organic chemistry in 2005.

Axel G. Griesbeck was born in the state of Hesse, Germany, in 1958. He studied chemistry at the University of Munich from 1976 and received his doctoral degree in 1984 on kinetic studies of singlet oxygen reactions (Prof. Klaus Gollnick). After three years as post-doc at the University of Würzburg (Prof. Waldemar Adam), the ETH Zürich (Prof. Dieter Seebach) and the Weizmann Institute of Science (Prof. Ernst Fischer), he performed his Habilitation in 1991 at the University of Würzburg. He was guest professor at the University of Wisconsin at Madison and the IMCR in Tsukuba, Japan. Since 1994 he is professor at the University of Cologne. He has published more than 180 papers on synthetic and mechanistic organic photochemistry and two books on organic photochemistry and is active in the fields of preparative and mechanistic organic photochemistry, photooxygenation, photocycloaddition and photo-induced electron transfer reactions. He received the Grammatikakis-Neumann prize in 1999 and is currently chairman of the photochemistry section of the German Chemical Society (GDCh).

Lars-Oliver Höinck was born in Cologne, Germany, in 1966. He studied chemistry at the University of Cologne and received his diploma degree in 2005. He is currently working on his doctoral thesis under the supervision of Prof. Axel G. Griesbeck. His research topic is the synthesis of hydrophilic antimalarial 1,2,4-trioxanes.

Johann Lex was born in Bottrop, a city near Essen, Germany, in 1942. He studied chemistry at the University of Cologne from 1963 to 1969 and received his doctoral degree in 1972 on X-ray structural investigations of heterocyclic sulfur compounds (Prof. Franz Feher) at the Institute of Inorganic Chemistry. After moving to the Institute of Organic Chemistry in 1978 he established and built up the X-ray department and determined numerous crystal structures, mainly derivatives of octalenes, annulenes, porphyrins and 'figure eight compounds' from the research group of Emanuel Vogel. He still continues his activities as service crystallographer at the University of Cologne.

Claus Miara was born in Bremerhaven, Germany, in 1974. He started studying chemistry 1995 at the Carl von Ossietzky University Oldenburg and moved in 1998 to the University of Cologne, where he finished his Diploma Thesis 2002. Currently, he is examining photooxygenation reactions and the use of polymer supports within the scope of his Ph.D. thesis under the supervision of Prof. Axel G. Griesbeck.

Jörg M. Neudörfl was born in Hürth, near Cologne in 1965. He studied chemistry at the University of Cologne from 1986 and received his doctoral degree in 2002 under the supervision of Prof. Otto Ermer on the structural chemistry of salts derived from mellitic acid and the inculsion behavior of hexaphenylbenzene hexacarboxylic acid. He is currently working as service crystallographer at the Institute of Organic Chemistry, University of Cologne.

which were obtained from emulsifier-free emulsion polymerization of styrene in the presence of PP-IX and divinylbenzene, were not as stable as the TSP-derived beads and gave rise to strong bleaching after 3–4 photooxygenation cycles. A scanning electron microscopy (SEM) picture of the former sample (unswollen) is shown in Figure 2.

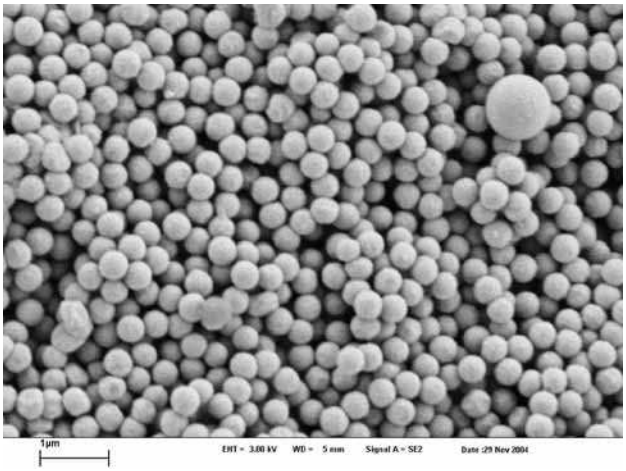
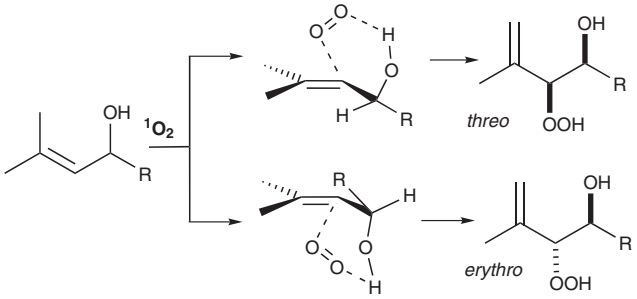


Figure 2 SEM pictures of protoporhyrin IX containing polymer beads.

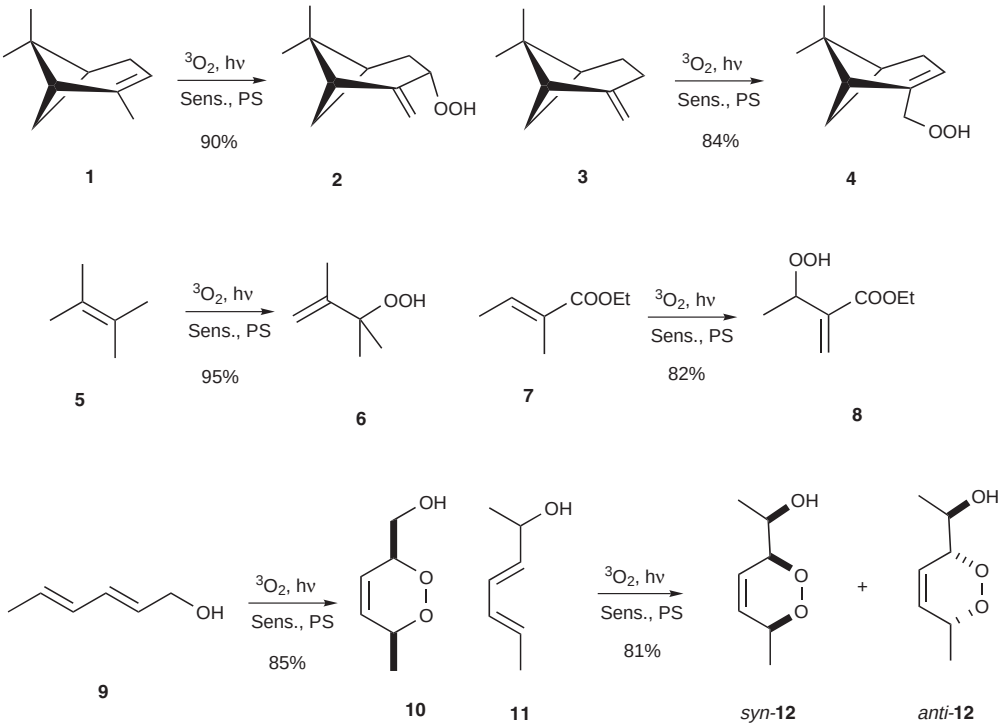
Some prototype reactions are illustrated in Scheme 1: the ene reactions of α- and β-pinene (**1** and **3**) to give the allylic hydroperoxides **2** and **4**, of 2,3-dimethylbut-2-ene (**5**) and ethyl tiglate (**7**) to the allylic hydroperoxides **6** and **8**, and the [4+2] cycloaddition of singlet oxygen to achiral and chiral dienes **9** and **11**. The *syn*/*anti* selectivity in **12** of the singlet oxygen addition to **11** was very low, in pronounced opposition to the reaction with monoalkenes.

Especially sensitive with regard to diastereoselectivity, however, is the singlet oxygen ene reaction with chiral allylic alcohols: when the reaction is performed in non-polar solvents, preferentially the *threo* isomers are formed with high diastereoselectivites (Scheme 2), in protic solvents the selectivities drop remarkably.[9] We used as a characteristic selectivity model the ene reaction of 4-methylpent-3-en-2-ol (mesitylol, **13**). The dr values were not only characteristic of the solvent but also on the initial concentration and the degree of conversion of the substrate. Additionally, H/D exchange in the starting material led to a decrease in selectivity (Scheme 3).

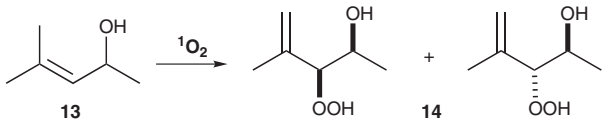


Scheme 2 Diastereoselectivity of the singlet oxygen ene reaction with chiral allylic alcohols.

These experiments did clearly provide evidence for non-covalent interactions between singlet oxygen and the sub-



Scheme 1 Prototype ene reactions and Diels–Alder type cycloadditions of alkenes and dienes with singlet oxygen in polystyrene (PS) matrix.



CCl_4, 4x10^{-2} M	93	:	7
CH_3OH, 4x10^{-2} M	73	:	27
CD_3OD, 4x10^{-2} M	68	:	32
PEG, max. loading	64	:	36
PS, max. loading (ld.)	75	:	25
PS, 1/$_{10}$ ld.	86	:	14
PS, 1/$_{10}$ ld., 20% conv.	90	:	10

Scheme 3 Diastereoselectivity of the mesitylol ene reaction; 100% conversion if not mentioned.

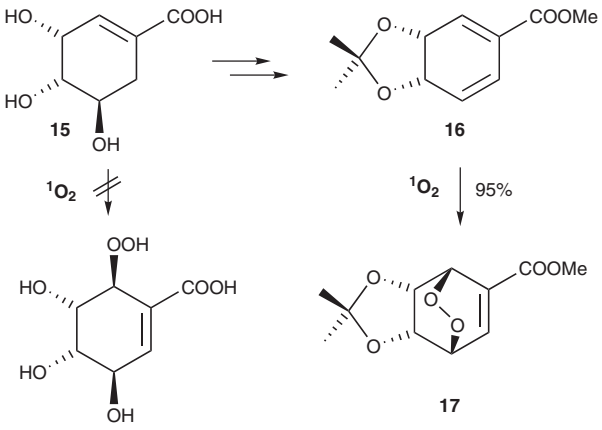
strate as well as the product of the ene reaction. At very high concentrations (e.g. under solvent-free conditions in polymeric matrices), the diastereoselectivity drops due to intermolecular hydrogen-bonding between substrate molecules; at higher degrees of conversion, the diastereoselectivity drops because of stronger hydrogen-bonding between the more polar β-hydroperoxy alcohols and the substrate. This complex reaction behavior could be nicely investigated in the polymeric reaction containers. Reducing the amount of substrate loaded to the polymer leads to increased selectivity at low conversions and again drops with increasing conversion.[10] The lowest diastereoselectivity was observed either in protic solvents or in polar polymer films such as poly(ethylene glycol) (PEG).

As already mentioned, we routinely use two approaches to singlet oxygen production and application to oxygenation: (a) a purely adsorptive approach where non-polar singlet oxygen sensitizers with high $^1O_2$ quantum yields are embedded into polymeric matrices by a wetting/drying process, and (b) covalent linking of functionalized sensitizer dye monomers during the polymerization process. In both cases, the polymer particles are subsequently swollen with the substrate dissolved in a volatile polar solvent (see experimental procedures).

Two Directing Effects: Two Case Studies

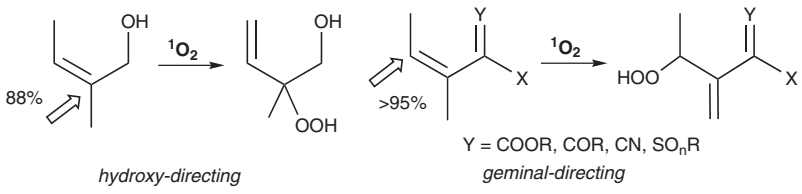
The *hydroxy-directing effect* has been extensively used for control of the regio- and diastereoselectivity of the ene reaction of singlet oxygen with chiral allylic alcohols: a hydroxy group in an allylic position directs the $^1O_2$ attack towards the proximate position of the C=C double bond and simultaneously a *syn* addition is enforced. On the other hand, the hydroxy group deactivates the alkene by a factor of roughly ten in comparison with the unsubstituted alkene.[9] The *geminal-directing effect* is a purely regiocontrolling phenomenon describing the ene reaction of $^1O_2$ with α,β-unsaturated carbonyl compounds and analogs with a substituent bearing allylic hydrogens at the α-carbon. To these compounds, $^1O_2$ adds preferentially to the β-carbon with concomitant hydrogen abstraction resulting in α-hydroperoxyalkyl acrylate derivatives (Scheme 4).[11]

We have now investigated substrates which combine these two effects in order to generate β-hydroperoxy alcohols with an additional acrylate function, substrates desired for the synthesis of potential antimalarials combining 1,2,4-trioxane (*vide infra*) with the acrylamide benzophenone-conjugate pharmacophors. The first substrate was shikimic acid (**15**), a cyclohexane carboxylic acid with a properly flanked hydroxyl group. The combination of the two deactivating groups together with the low solubility in less polar solvents, however, completely prevented $^1O_2$ addition. A straightforward way to activate the substrate was the transformation into the acetal-protected diene **16**. Cycloaddition with $^1O_2$ resulted in the endoperoxide **17** which could be further modified (Scheme 5).[12]



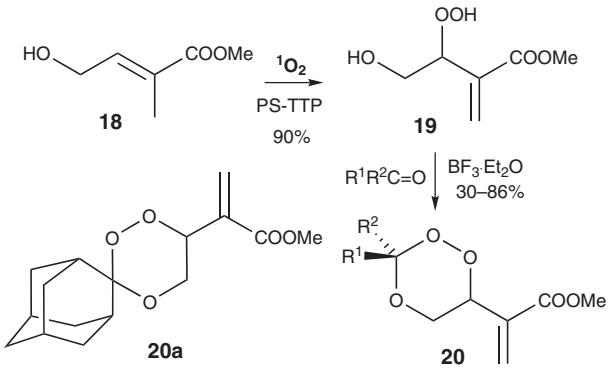
Scheme 5 Intended photooxygenation of shikimic acid **15** and its derivative **16**.

The second substrate was the 4-hydroxy tiglate **18** obtained from the 'C_5-aldehyde' (an important intermediate in the industrial synthesis of vitamin A).[13] This compound reacted slowly with singlet oxygen to give the allylic hydroperoxide **19** with high regioselectivity. This compound



Scheme 4 Regioselectivity control by hydroxy and gem effects.

was converted into trioxanes **20** by Lewis acid catalyzed peroxyacetalization with ketones (Scheme 6).[14] Adamantanone as the carbonyl component gave the spiroperoxide **20a** that was also analyzed by X-ray crystal determination.[14] One major driving force for introducing acrylate side-chains to the 1,2,4-trioxane skeleton was a recent report on the antimalarial activity of acrylamide-benzophenone conjugates[15] which we currently try to compare with acrylate-trioxane conjugates. The cooperative directing of hydroxy and gem effect in **18** is thus a valuable tool for the synthesis of properly substituted hydroperoxides.



Scheme 6 Photooxygenation of the allylic alcohol **18** and subsequent trioxane synthesis.

Synthesis of 1,2,4-Trioxanes Using the Photooxygenation Route

The quest for the synthesis of a broad series of structurally diverse compounds with a central 1,2,4-trioxane skeleton results from the ongoing struggle for active and reliable antimalarials which do not show resistance against the most problematic form of *Malaria tropica*, resulting from infection by the *Plasmodium falciparum* parasite.[16] There are numerous potential drugs and derivatives which are currently investigated. Besides the well established quinoline derivatives, compounds that are currently tested as pharmaceutical leads include those that interact with different locations of infected erythrocytes. Classes of compounds having in common the structural motif of cyclic peroxides play a special role both because of their structures and the possible mode of action. Many of these compounds are structurally derived from the naturally occurring sesquiterpene lactone artemisinin (qinghaosu), a compound with a 1,2,4-trioxane core structure (Figure 3).[17] But also 1,2-dioxanes as present in yingzhaosu A and C show high antimalarial activities.[18]

Extensive work has been published on the total synthesis of artemisinin,[19] the preparation of its derivatives[20] as well as on the elucidation of the peroxide-specific mode of action.[21] Semisynthetic derivatives have been reported from several research groups as well as fully synthetic spirobicyclic peroxides and 'dual systems', with 1,2,4-trioxanes linked to quinolines.[22] One straightforward process is the introduction of a hydroperoxy group β to a preexisting hydroxy substituent or *vice versa*. The best process for this goal is the singlet oxygen ene reaction with allylic alcohols directed by the hydroxy effect regio- and diastereoselectively. The subsequent peroxyacetalization can be catalyzed by Brönsted[23] or Lewis acids[24] such as concentrated sulfuric acid or boron trifluoride, respectively (Scheme 7).

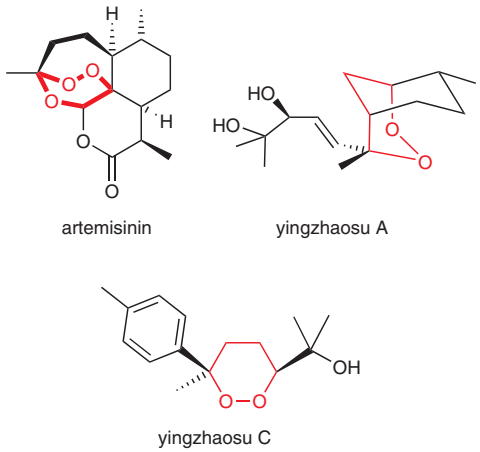
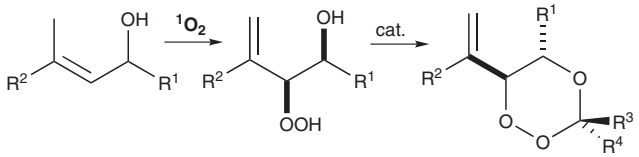


Figure 3 Natural antimalarials: artemisinin, yingzhaosu A and C.

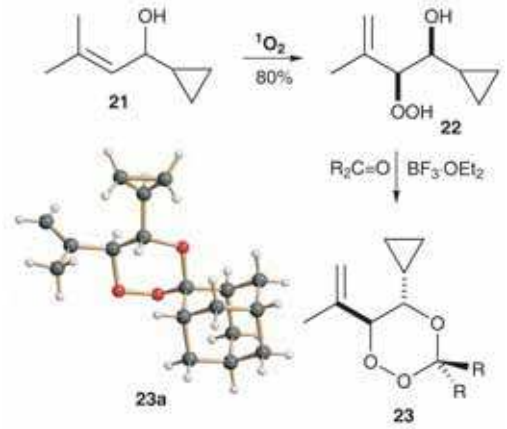


Scheme 7 Access to 1,2,4-trioxanes by the singlet oxygen route.

Peroxyacetalization with Symmetric Ketones

The photooxygenation of chiral allylic alcohols in polymer matrices delivers the β-hydroxy allylic hydroperoxides in moderate diastereoselectivity but in good yields and with much less impurities than the traditional solution-phase reaction. When treating these products with symmetric ketones in the presence of catalytic amounts of BF_3, the *trans* 5,6-substituted 1,2,4-trioxanes were formed in good to moderate yields. Volatile ketones such as acetone, cyclopentanone or cyclohexanone were applied in 10–20-fold excess and high yields of trioxanes were obtained. More problematic was the use of adamantanone which was applied in stoichiometric amounts and complicated product separation.

A typical reaction protocol is shown in Scheme 8: the cyclopropane **21** is available from aldol condensation of cyclopropylmethylketone with acetone,[25] photooxygenation in polymer beads results in a 62:38 mixture of diastereoisomeric hydroperoxides **22** in 80% yield (combined, only the major isomer shown). Subsequent treatment with 1–20 equivalents of ketone in the presence of catalytic BF_3 afforded the trioxanes **23** in yields of 8–41% (adaman-

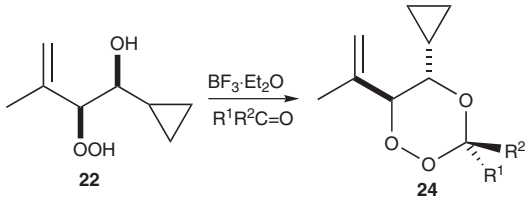


Scheme 8 5-Cyclopropanated 1,2,4-trioxanes, for R and yields see text; X-ray structure of **23a** (for X-ray data, see Table 1 in experimental part).

tanone: 8%, cyclohexane-1,4-dione: 17%, acetone: 41%). In most cases, the trioxane resulting from the minor hydroperoxide diastereomer could not be isolated after purification. The currently most active trioxane of this series in the antimalarial *in vitro* test against *P. falciparum* was compound **23a**.[26]

Non-Symmetric Ketones and Aldehydes

When using non-symmetric ketones or aldehydes, a third stereogenic center was created at C-3. In most cases the configuration of this center was perfectly controlled during the reaction with the major diastereoisomeric (*threo*) hydroperoxides. In these cases, the products (e.g. in Scheme 9 the trioxanes **24** from the cyclopropyl derivative **22**) were formed as sole diastereoisomers in an all-equatorial substituent pattern (from NOE measurements). The yields with aliphatic aldehydes were generally low due to competitive 1,3,5-trioxane formation and could be increased by using acetal derivatives. Orthoesters could also be applied and gave rise to different stereochemical results (C3-OR in an axial position) indicating strong anomeric effects (*vide infra*).



	R^1	R^2	yield	dr
a	Et	Me	62%	72:28
b	Et	H	21%	> 98:2

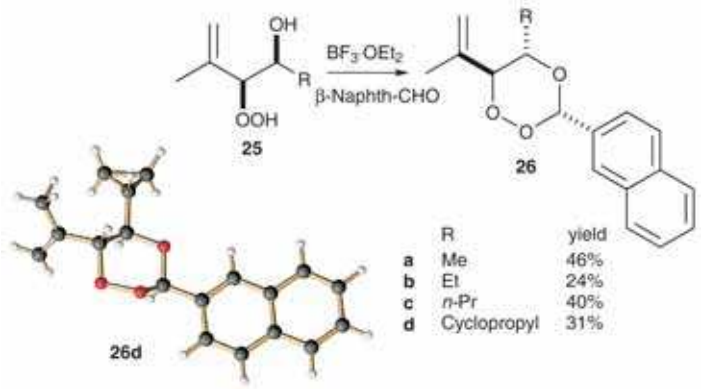
Scheme 9 C-4 chiral, 5-cyclopropanated 1,2,4-trioxanes from **22**.

The C3-Naphthyl Series

A special feature in the peroxyacetalization runs was the application of naphthaldehyde derivatives. These experiments were performed in order to approach trioxane-quinoline conjugates that might act cooperatively in their antimalarial activities. Therefore, we investigated the reaction of β-hydroperoxy alcohols with β-naphthaldehyde (equimolar amounts) as a model compound and obtained the corresponding trioxanes in good yields indicating that the reactivity of the naphthaldehyde was higher than in the adamantanone series (Scheme 10).

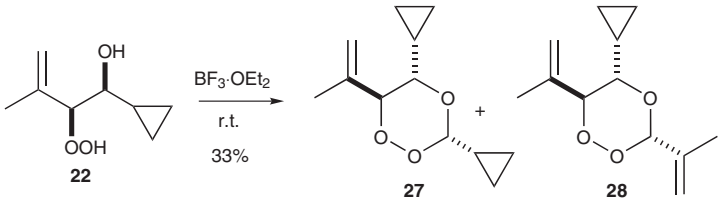
Acid-Catalyzed Cleavage Followed by Cross-Peroxy Acetalization

Lewis- and Brönsted acids slowly decompose β-hydroxy allylic hydroperoxides in a Hock-type cleavage to give two carbonyl fragments. This reaction can efficiently compete with the regular peroxyacetalization as described above if (a) sterically demanding carbonyl compounds are used and/or (b) only stoichiometric amounts of the carbonyl compounds could be used. In case of adamantanone both effects act cooperatively and the yields of spiroadamantane peroxides were generally low. On the other hand, controlled acid-catalyzed peroxide cleavage in the absence of external carbonyls generates minute amounts of



	R	yield
a	Me	46%
b	Et	24%
c	*n*-Pr	40%
d	Cyclopropyl	31%

Scheme 10 3-β-Naphthyl-substituted 1,2,4-trioxanes, X-ray structure of **26d** (for X-ray data, see Table 1 in experimental part).



Scheme 11 Lewis acid catalyzed cleavage and cross-peroxyacetalization of the β-hydroxy hydroperoxide **22**.

carbonyl fragments in the presence of the β-hydroxy hydroperoxides and thus cross-peroxyacetalization is initiated. This process allows the access to a series of new trisubstituted 1,2,4-trioxanes with high diastereoselectivitiy. A typical example is shown in Scheme 11 with the BF_3-catalyzed decomposition of the cyclopropyl derivative **22**.

Bis-Trioxanes: Doubled Peroxyacetalization

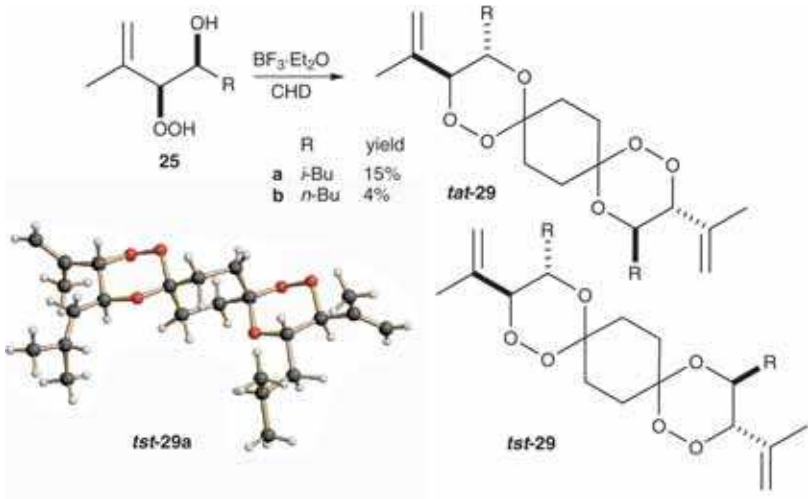
The peroxyacetalization of 1,2-hydroperoxy alcohols with cyclohexane-1,4-dione has been already investigated by several research groups including us (see compounds **23**).[22,27] In all cases reported in literature, the second carbonyl group was used as anchor functionality for introducing amino groups, e.g. for the synthesis of the dual trioxaquines developed by the Meunier group.[22,27b] The bifunctional ketone can in principle also be used as a basis for the synthesis of dispiroperoxides by application of an excess of hydroperoxide. The yields for these processes were in all cases low (4–20%) and diastereoisomeric mixtures of dispiroperoxides **29** were isolated (Scheme 12).[28] The X-ray structure analyses revealed that the *syn* compounds have the two peroxide bridges freely exposed to one side of the molecule and might therefore exhibit interesting pharmacological properties. Highly active antimalarial trioxane dimers have already been synthesized from artemisinin derivatives by bridging reactions.[29]

A Diverse Family of 1,2,4-Trioxanes

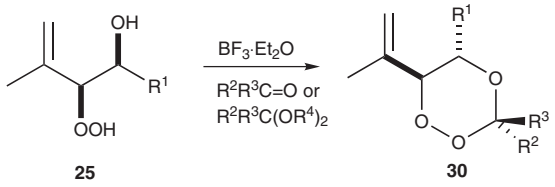
Following the procedures described above, a family of mono-, bi-, spiro- and dispirocyclic 1,2,4-trioxanes were generated in recent years. A sample collection is shown in Scheme 13, demonstrating that a broad substituent pattern is available at positions C3 and C5 of the 1,2,4-trioxane ring. The two methods already mentioned are also compared here: the trans-peroxyacetalization of acetals (Method B, for the synthesis of trioxanes **30a**) is superior over the direct use of volatile aldehydes (Method A). This method is also described for the synthesis of the 1,2,4-trioxane **24b** in the experimental section. When triethyl orthoformate was used as component, the first examples of orthoperacetals with the trioxane substructure (e.g. **30g** as a 3:1 diastereoisomeric mixture) were obtained in excellent yields.

Polymer-Bound Porphyrin Dyes; PP-S-DVB; Typical Procedure

Deionized H_2O (200 mL), acidified with H_2SO_4 to pH 2.3, was purged with N_2 and heated to 70 °C for 20 min in a 500-mL three-necked flask equipped with a stopper, a reflux condenser and a gas inlet. Subsequently, freshly distilled styrene (10 g), divinylbenzene (DVB, 100 mg) and protoporphyrin IX (10 mg) were added rapidly and the system was sealed in order to prevent contamination with air. While the mixture was being vigorously stirred, potassium peroxodisulfate (120 mg) in H_2O (10 mL) was added at once. As the polymerization proceeds, the color of the reaction mixture turned



Scheme 12 Synthesis of dispiro compounds **29** from cyclohexane-1,4-dione (CHD) and **25**, X-ray structure of ***tat*-29a** (for X-ray data, see Table 1 in experimental part).



25 30

	R1	R2	R3	R4	yield
a	*n*-Bu	Ph	H	Me	48%
b	*i*-Bu	ß-Naph	H	-	21%
c	Me	- Ada -		-	10%
d	*i*-Bu	- Ada -		-	12%
e	Me	Fu	H	-	34%
f	Et	o-Cl-Ph	H	-	22%
g	Me	OEt	H	OEt	70%

Scheme 13 Diverse 1,2,4-trioxane structures from reaction of 1,2-hydroperoxy alcohols with ketones and aldehydes (Method A) or acetals and orthoesters (Method B).

faint red and after a polymerization period of 7–9 h, the mixture was quenched with MeOH (200 mL) and then cooled to r.t. The polymer particles were separated by centrifugation at 3500 rpm, and any free (non-polymerized) sensitizer particles were removed by extraction with CH_2Cl_2 several times, until the dye in the washing solvent was no longer detectable. The beads were dried at 40 °C under vacuum to afford 3.25 g (33%) of the polymer-bound sensitizer. PP-S-DVB was obtained as a sandy solid.

Photooxygenation Using Polymer-Bound Porphyrin Dyes as Sensitizers as well as Reaction Media; Solvent-Free Photooxygenation Conditions

***a.* Using Commercial PS-DVB Copolymer**

The polymer particles (ca. 2–3 g) were distributed in a petri dish (19 cm diameter) and were swollen with CH_2Cl_2 (20 mL). The substrate (ca. 10 mmol) and the nonpolar sensitizer (TPP or TTP, ca. 3–6 mg) in EtOAc (20 mL) were subsequently added and the excess solvent was evaporated by leaving the petri dish in a well ventilated hood. The petri dish was covered with a glass plate and the sandy solid was irradiated with halogen lamp or sodium street lamp. The polymer beads were subsequently rinsed with EtOH (3 × 30 mL) and filtered (the beads were kept for regeneration and reuse). The solvent was evaporated under reduced pressure (**Caution!** water bath temperature should not exceed 30 °C) and the composition of the product was determined by ^{1}H as well as ^{13}C NMR spectroscopy.

***b.* Using Synthesized PP-S-DVB Copolymers**

The dye-cross-linked polymer beads (TSP-S-DVB or PP-S-DVB, ca. 0.60 g) in a petri dish (14 cm in diameter) were swollen with CH_2Cl_2 (20 mL), then the substrate (ca. 5 mmol) in EtOAc (20 mL) was added. Subsequent treatment as described before afforded the product.

(1*RS*,2*RS*)-1-Cyclopropyl-2-hydroperoxy-3-methylbut-3-en-1-ol (*threo*-22)

Photooxygenation of **21** (1.0 g, 7.94 mmol) for 60 h afforded a diastereomeric mixture (dr: *syn*:*anti*, 62:38) of β-hydroxy allylic hydroperoxides **22** (1.0 g, 80%) as a colorless oil.

***threo*-22, Major Isomer**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.20–0.52 (m, 4 H, CH_2CH_2), 0.78–0.99 (m, 1 H, CH), 1.75 (m, 3 H, CH_3C=), 3.07 (dd, 1 H, *J* = 8.0, 8.0 Hz, C*H*OH), 4.29 (d, 1 H, *J* = 9.3 Hz, C*H*OOH), 5.05 (m, 2 H, CH_2=C).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 1.8 (t, *C*H_2CH_2), 3.2 (t, *C*H_2CH_2), 14.0 (d, CH), 18.9 (q, *C*H_3C=), 75.0 (d, *C*HOH), 93.3 (d, *C*HOOH), 115.5 (t, *C*H_2=C), 141.6 (s, *C*=CH_2).

(1*RS*,2*SR*)-1-Cyclopropyl-2-hydroperoxy-3-methylbut-3-en-1-ol; Minor Isomer

^{1}H NMR (300 MHz, $CDCl_3$): δ (additional significant signals) = 1.82 (m, 3 H, CH_3C=), 3.14 (dd, 1 H, *J* = 4.3, 8.8 Hz, C*H*OH), 4.41 (d, 1 H, *J* = 4.3 Hz, C*H*OOH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 2.6 (t, *C*H_2CH_2), 2.9 (t, *C*H_2CH_2), 13.3 (d, CH), 19.6 (q, *C*H_3C=), 75.6 (d, *C*HOH), 91.2 (d, *C*HOOH), 115.4 (t, *C*H_2=C), 141.3 (s, *C*=CH_2).

The diastereomeric mixture of allylic hydroperoxides was applied for peroxyacetalization without further purification.

(5′*RS*,6′*RS*)-5′-Cyclopropyl-6′-(prop-1-en-2-yl)-spiro{tricyclo[3.3.1.1^{3,7}]decane-2,3′-[1,2,4]-trioxane} (23a)

A solution of **22** (1.88 g, 11.9 mmol) and adamantanone (1.78 g, 11.9 mmol) in CH_2Cl_2 were treated with catalytic amounts of $BF_3{\cdot}OEt_2$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EtOAc–*n*-hexane, 1:10, R_f 0.81) afforded the pure 1,2,4-trioxane **23a** as a faint yellow oil which crystallized upon standing (0.25 g, 8%); mp 79–81 °C.

IR (film): 3079, 2931, 2917, 1653, 1112, 1079, 1025, 926, 910, 891 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.31–0.49 (m, 4 H, CH_2CH_2), 0.78 [m, 1 H, C*H*(CH_2)$_2$], 1.50–2.19 (m, 13 H, CH and CH_2), 1.79 (m, 3 H, CH_3C=), 2.82 (m, 1 H, CH), 3.33 (dd, 1 H, *J* = 7.4, 9.4 Hz, OCH), 4.38 (d, 1 H, *J* = 9.4 Hz, OOCH), 5.04 (m, 2 H, CH_2=).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 1.9 (t, CH_2), 3.1 (t, CH_2), 12.2 [d, *C*H(CH_2)$_2$], 21.0 (q, *C*H_3C=), 27.5 (d, CH), 27.6 (d, CH), 30.2 (d, CH), 36.9 (d, CH), 33.4 (t, CH_2), 33.7 (t, CH_2), 33.8 (t, CH_2), 34.0 (t, CH_2), 37.6 (t, CH_2), 73.0 (d, OCH), 87.9 (d, OOCH), 105.0 (s, OCOO), 117.2 (t, CH_2=), 140.4 (s, *C*=CH_2).

MS (EI, 70 eV): *m*/*z* (%) = 290 (M^+, <1), 220 ($M^+ - C_4H_6O$, 1), 150 ($C_{10}H_{14}O^+$, 57), 108 ($C_8H_{12}^+$, 47), 93 ($C_7H_9^+$, 57), 81 ($C_6H_9^+$, 37), 80 ($C_6H_8^+$, 97), 79 ($C_6H_7^+$, 100), 67 ($C_5H_7^+$, 32), 55 ($C_3H_3O^+$, 27).

Anal. Calcd for $C_{18}H_{26}O_3$ (290.40): C, 74.45; H, 9.02. Found: C, 73.61; H, 8.94.

(3*RS*,5*RS*,6*RS*)-5-Cyclopropyl-3-(naphth-2-yl)-6-(prop-1-en-2-yl)-1,2,4-trioxane (26d)

A solution of **25** (1.25 g, 7.91 mmol) and β-naphthaldehyde (1.23 g, 7.88 mmol) in CH_2Cl_2 were treated with catalytic amounts of $BF_3{\cdot}OEt_2$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EtOAc–*n*-hexane, 1:10, R_f 0.67) afforded the pure 1,2,4-trioxane **26d** as a yellow oil which crystallized upon standing (0.72 g, 31%).

IR (film): 3088, 3011, 2968, 2934, 1647, 1603, 1126, 1071, 904, 859, 814 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.39–0.64 (m, 4 H, CH_2CH_2), 0.98 [m, 1 H, C*H*(CH_2)$_2$], 1.87 (m, 3 H, CH_3C=), 3.44 (dd, 1 H, *J* = 7.4, 9.1 Hz, OCH), 4.68 (d, 1 H, *J* = 9.1 Hz, OOCH), 5.14 (m, 2 H, CH_2=), 6.31 (s, 1 H, OCHOO), 7.46–7.98 (m, 7 H_{arom}).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 2.0 (t, CH_2), 2.8 (t, CH_2), 11.6 [d, *C*H(CH_2)$_2$], 20.7 (q, *C*H_3C=), 81.0 (d, OCH), 87.8 (d, OOCH), 104.0 (d, OCHOO), 117.5 (t, CH_2=), 124.2 (d, CH_{arom}), 126.2 (d, CH_{arom}), 126.7 (d, CH_{arom}), 127.0 (d, CH_{arom}), 127.7 (d, CH_{arom}), 128.2 (d, CH_{arom}), 128.5 (d, CH_{arom}), 131.8 (s, C_{arom}), 132.9 (s, C_{arom}), 134.1 (s, C_{arom}), 139.9 (s, *C*=CH_2).

HRMS (EI, 70 eV): $C_{19}H_{20}O_3$: calcd: M = 296.141 g/mol; found: M = 296.141 ± 0.005 g/mol.

Anal. Calcd for $C_{19}H_{20}O_3$ (296.37): C, 77.00; H, 6.80. Found: C, 76.47; H, 6.83.

Lewis Acid Catalyzed Cleavage of β-Hydroxy Hydroperoxides and Subsequent Cross-Peroxyacetalization Reaction; General Procedure

To a stirred solution of appropriate β-hydroxy hydroperoxide in anhydrous CH_2Cl_2 (100 mL) was added at r.t. catalytic amounts of $BF_3{\cdot}OEt_2$ (ca. 0.2 mL) and the mixture was further stirred for 12 h at r.t. The mixture was partitioned between CH_2Cl_2 and aq sat. $NaHCO_3$ solution and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were washed with brine, H_2O, and dried (Na_2SO_4). Solvent evaporation (water bath temperature should not exceed 30 °C) followed by chromatographic purification afforded the pure 1,2,4-trioxanes.

(3*RS*,5*RS*,6*RS*)-3,5-Dicyclopropyl-6-(prop-1-en-2-yl)-1,2,4-trioxane (27)

Following the above procedure, from 1-cyclopropyl-2-hydroperoxy-3-methylbut-3-en-1-ol (**22**; 1.50 g, 9.5 mmol) was obtained after usual work-up, the crude 1,2,4-trioxanes **27** and **28** as a mixture in a ratio of 61:39 (0.66 g, 33%). The yellow oil was then purified by preparative thick-layer chromatography (SiO_2, EtOAc–*n*-hexane, 1:10, R_f 0.81) to give the 1,2,4-trioxane **27** (0.23 g, 12%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.24–0.59 (m, 8 H, 4 CH_2), 0.74–0.95 (m, 2 H, 2 CH), 1.77 (s, 3 H, CH_3C=), 3.06 (dd, 1 H, *J* = 7.9, 8.7 Hz, OCH), 4.45 (d, 1 H, *J* = 9. 2 Hz, OOCH), 4.73 (d, 1 H, *J* = 6.2 Hz, OCHOO), 5.04 (br s, 2 H, CH_2=C).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 1.4 (t, *C*H_2CH), 1.7 (t, *C*H_2CH), 1.9 (t, *C*H_2CH), 2.8 (t, *C*H_2CH), 11.5 [d, *C*H(CH_2)$_2$], 12.0 [d, *C*H(CH_2)$_2$], 20.6 (q, *C*H_3C=), 80.8 (d, OCH), 87.4 (d, OOCH), 106.4 (d, OCHOO), 117.1 (t, *C*H_2=C), 139.4 (s, *C*=CH_2).

(3*RS*,5*RS*,6*RS*)-5-Cyclopropyl-3,6-di(prop-1-en-2-yl)-1,2,4-trioxane (28)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.17–0.52 (m, 4 H, CH_2CH_2), 0.67–1.24 [m, 1 H, C*H*(CH_2)$_2$], 1.69 (m, 3 H, CH_3C=), 1.74 (t, 3 H, *J* = 1.2 Hz, CH_3C=), 3.21 (dd, 1 H, *J* = 7.1, 9.0 Hz, OCH), 4.43 (d, 1 H, *J* = 9.1 Hz, OOCH), 4.98–5.04 (m, 3 H, CH_2=C), 5.18 (br s, 1 H, CH_2=C), 5.45 (s, 1 H, OOCHO).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 1.5 (t, CH_2), 2.3 (t, CH_2), 11.3 [d, *C*H(CH_2)$_2$], 17.5 (q, *C*H_3C=), 20.4 (q, *C*H_3C=), 79.8 (d, OCH), 87.5 (d, OOCH), 104.5 (d, OOCHO), 116.5 (t, *C*H_2=C), 117.2 (t, *C*H_2=C), 138.7 (s, *C*=CH_2), 139.2 (s, *C*=CH_2).

(3*RS*,4*RS*,12*RS*,13*RS*)-4,13-Diisobutyl-3,12-diisopropenyl-1,2,5,10,11,14-hexaoxadispiro[5.2.5.2]hexadecane (*tst*-29a) and (3*RS*,4*RS*,12*SR*,13*SR*)-4,13-diisobutyl-3,12-diisopropenyl-1,2,5,10,11,14-hexaoxadispiro[5.2.5.2]hexadecane (*tat*-29a)

A solution of **25** (R = *i*-Bu) (1.32 g, 7.59 mmol) and cyclohexan-1,4-dione (0.42 g, 3.75 mmol) in CH_2Cl_2 were treated with a catalytic amount of $BF_3{\cdot}Et_2O$ (0.2 mL). Usual work-up followed by preparative thick-layer chromatography (SiO_2, EtOAc/*n*-hexane, 1:10, R_f 0.71) afforded a diastereomeric mixture of the 1,2,4-trioxanes **29a** in a ratio of 1:1 (0.23 g, 15%) as an oil which crystallizes on standing.

^{1}H NMR: (300 MHz, $CDCl_3$, both diastereomers) δ = 0.81–0.94 (m, 6 H, (C*H*$_3$)$_2$CH), 1.06 (m, 1 H, C*H*$_2$CH), 1.33 (m, 1 H, C*H*$_2$CH), 1.59–1.89 (m, 3 H, C*H*$_2$ and C*H*CH_2), 1.72 (m, 3 H, C*H*$_3$C=), 2.10–2.35 (m, 2 H, C*H*$_2$), 3.97 (m, 1 H, OC*H*), 4.24 (d, 1 H, *J* = 9.54 Hz, OOC*H*), 5.05 (m, 2 H, C*H*$_2$=C).

^{13}C NMR: (75.5 MHz, $CDCl_3$, 1st diastereomer) δ = 19.7 (q, *C*H_3C=), 21.3 (q, *C*H_3CH), 23.5 (d, *C*HCH_2), 23.7 (q, *C*H_3CH), 25.2 (t, CH_2), 31.2 (t, CH_2), 39.6 (t, CH_2CH), 67.8 (d, OCH), 88.1 (d, OOCH), 102.3 (s, OCOO), 118.2 (t, *C*H_2=C), 139.0 (s, *C*=CH_2); Additional signals of 2nd diastereomer: δ = 19.6 (q, *C*H_3C=), 23.5 (d, *C*HCH_2), 24.7 (t, CH_2), 30.7 (t, CH_2), 39.6 (t, *C*H_2CH), 88.1 (d, OOCH), 102.3 (s, OCOO), 139.0 (s, *C*=CH_2).

(3*RS*,4*RS*,12*RS*,13*RS*)-4,13-Dibutyl-3,12-diisopropenyl-1,2,5,10,11,14-hexaoxadispiro[5.2.5.2]hexadecane (*tst*-29b) and (3*RS*,4*RS*,12*SR*,13*SR*)-4,13-Dibutyl-3,12-diisopropenyl-1,2,5,10,11,14-hexaoxadispiro[5.2.5.2]hexadecane (*tat*-29b)

A solution of **25** (R = *n*-Bu) (1.45 g, 8.33 mmol) and cyclohex-1,4-dione (0.46 g, 4.11 mmol) in CH_2Cl_2 were treated with catalytic amounts of $BF_3{\cdot}OEt_2$ (0.2 mL). Usual work-up followed by preparative thick-layer chromatography (SiO_2, EtOAc–*n*-hexane, 1:10, R_f 0.53) afforded a diastereomeric mixture of the pure 1,2,4-trioxanes **29b** in a ratio 1:1 (0.07 g, 4%) as an oil which crystallized on standing.

First Diastereomer (*tst*-29b)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, 3 H, *J* = 7.1 Hz, C*H*$_3$CH$_2$), 1.05–1.72 (m, 8 H, CH_2), 1.60 (m, 3 H, CH_3C=), 2.20 (m, 2 H, CH_2), 3.86 (m, 1 H, OCH), 4.25 (d, 1 H, *J* = 9.6 Hz, OOCH), 5.04 (s, 2 H, CH_2=).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.9 (q, *C*H_3CH$_2$), 19.7 (q, *C*H_3C=), 22.5 (t, *C*H_2CH$_3$), 25.2 (t, CH_2), 27.0 (t, *C*H_2CH$_2$), 30.4 (t, *C*H_2CH$_2$), 30.8 (t, CH_2), 69.8 (d, OCH), 87.7 (d, OOCH), 102.4 (s, OCOO), 118.1 (t, *C*H_2=C), 139.2 (s, *C*=CH_2).

Second Diastereomer (*tat*-29b)

IR (film): 3083, 2957, 2873, 1648, 1455, 1373, 1258, 1105, 1007, 928, 911 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, 3 H, *J* = 7.1 Hz, C*H*$_3$CH$_2$), 1.05–1.72 (m, 8 H, CH_2), 1.60 (m, 3 H, CH_3C=), 2.20 (m, 2 H, CH_2), 3.86 (m, 1 H, OCH), 4.25 (d, 1 H, *J* = 9.6 Hz, OOCH), 5.04 (s, 2 H, CH_2=).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.9 (q, *C*H_3CH$_2$), 19.8 (q, *C*H_3C=), 22.5 (t, *C*H_2CH$_3$), 24.9 (t, CH_2), 27.1 (t, *C*H_2CH$_2$), 30.5 (t, *C*H_2CH$_2$), 31.2 (t, CH_2), 69.8 (d, OCH), 87.7 (d, OOCH), 102.3 (s, OCOO), 118.1 (t, *C*H_2=C), 139.1 (s, *C*=CH_2).

Anal. Calcd for $C_{24}H_{40}O_6$ (424.57): C, 67.89, H, 9.50. Found: C, 67.43; H, 9.37.

Lewis Acid Catalyzed Transperoxyacetalization; (3*RS*,5*RS*,6*RS*)-5-Cyclopropyl-3-ethyl-6-(prop-1-en-2-yl)-1,2,4-trioxane (24b); Typical Procedure (Method B)

A solution of **22** (1.20 g, 7.59 mmol) and propionaldehyde diethyl acetal (1.0 g, 7.58 mmol) in CH_2Cl_2 were treated with catalytic amounts of $BF_3{\cdot}OEt_2$ (0.2 mL). Usual work-up and further purification of the crude product (0.67 g, 45%) by preparative thick-layer chromatography (SiO_2, EtOAc–*n*-hexane, 1:10, R_f 0.76) afforded a colorless oil composed of a diastereomeric mixture of the pure 1,2,4-trioxane **24b** as the major product, and **27**, **28** as minor products (315 mg, 21%).

IR (film): 3085, 3009, 2973, 2927, 2881, 1653, 1648, 1116, 1088, 1047, 943, 904 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (major product a) = 0.31–0.62 (m, 4 H, CH_2CH_2), 0.79 [m, 1 H, C*H*(CH_2)$_2$], 0.90 (t, 3 H, *J* = 7.5 Hz, C*H*$_3$CH$_2$), 1.56 (dq, 2 H, *J* = 5.3, 7.5 Hz, C*H*$_2$CH$_3$), 1.75 (m, 3 H, CH_3C=), 3.08 (dd, 1 H, *J* = 7.7, 9.1 Hz, OCH), 4.41 (d, 1 H, *J* = 9.1 Hz, OOCH), 5.01 (m, 2 H, CH_2=), 5.08 (t, 1 H, *J* = 5.4 Hz, OCHOO).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ (major product a) = 1.6 (t, CH_2), 2.6 (t, CH_2), 8.1 (q, *C*H_3CH$_2$), 11.4 [d, *C*H(CH_2)$_2$], 20.4 (q, *C*H_3C=), 25.3 (t, *C*H_2CH$_3$), 80.3 (d, OCH), 87.6 (d, OOCH), 105.1 (d, OCHOO), 117.0 (t, *C*H_2=C), 139.3 (s, *C*=CH_2).

Anal. Calcd for $C_{11}H_{18}O_3$ (198.26): C, 66.64; H, 9.15. Found: C, 66.55; H, 9.15.

(3*RS*,5*RS*,6*RS*)-5-Butyl-3-phenyl-6-(prop-1-en-2-yl)-1,2,4-trioxane (30a) (Method B)

A solution of **25** (R = *n*-Bu) (1.32 g, 7.59 mmol) and benzaldehyde dimethyl acetal (1.15 g, 7.57 mmol) in CH_2Cl_2 were treated with catalytic amounts of $BF_3{\cdot}OEt_2$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EtOAc–*n*-hexane, 1:10, R_f 0.76) afforded the pure 1,2,4-trioxane **30a** (0.96 g, 48%) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$CH$_2$), 1.23–1.61 (m, 6 H, CH_2), 1.80 (m, 3 H, C*H*$_3$C=), 3.92 (m, 1 H, OCH), 4.54 (d, 1 H, *J* = 9.3 Hz, OOCH), 5.13 (m, 1 H, CH_2=), 5.16 (s, 1 H, CH_2=), 6.22 (s, 1 H, OCHOO), 7.37–7.54 (m, 5 H_{arom}).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.9 (q, *C*H$_3$CH$_2$), 19.7 (q, *C*H$_3$C=), 22.6 (t, *C*H$_2$CH$_3$), 27.0 (t, *C*H$_2$CH$_2$), 30.1 (t, *C*H$_2$CH$_2$), 77.3 (d, OCH), 87.6 (d, OOCH), 104.0 (d, OCHOO), 118.5 (t, *C*H$_2$=C), 126.9 (d, CH_{arom}), 128.3 (d, CH_{arom}), 129.7 (d, CH_{arom}), 134.6 (s, C_{arom}), 138.8 (s, *C*=CH$_2$).

MS (EI, 70 eV): *m*/*z* (%) = 262 (M^+, not observed), 124 ($C_9H_{16}^+$, 13), 106 ($C_7H_6O^+$, 32), 105 ($C_7H_5O^+$, 100), 77 ($C_6H_5^+$, 33), 51 ($C_4H_3^+$, 13).

Anal. Calcd for $C_{16}H_{22}O_3$ (262.34): C, 73.25; H, 8.45. Found: C, 73.11; H, 8.46.

(3*RS*,5*RS*,6*RS*)-5-Isobutyl-3-(naphthalen-2-yl)-6-(prop-1-en-2-yl)-1,2,4-trioxane (30b) (Method A)

A solution of **25** (R = *i*-Bu) (1.21 g, 6.95 mmol) and β-naphthaldehyde (1.09 g, 6.99 mmol) in CH_2Cl_2 was treated with catalytic amounts of $BF_3{\cdot}OEt_2$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EtOAc–*n*-hexane, 1:10, R_f 0.71) afforded the 1,2,4-trioxane **30b** (0.46 g, 21%) as an oil which crystallized on standing to a white solid; mp 60–62 °C.

IR (CsI): 3095, 2956, 2934, 1605, 1347, 1098, 1080, 997, 863, 817 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, 3 H, *J* = 6.6 Hz, C*H*$_3$CH), 1.04 (d, 3 H, *J* = 6.8 Hz, C*H*$_3$CH), 1.33 (m, 1 H, C*H*$_2$CH), 1.70 (m, 1 H, C*H*$_2$CH), 1.87 (s, 3 H, C*H*$_3$C=), 2.08 (m, 1 H, C*H*CH$_2$), 4.12 (ddd, 1 H, *J* = 2.3, 9.1, 10.3 Hz, OCH), 4.65 (d, 1 H, *J* = 9.1 Hz, OOCH), 5.19 (m, 1 H, CH_2=), 5.24 (m, 1 H, CH_2=), 6.45 (s, 1 H, OCHOO), 7.49–8.07 (m, 5 H_{arom}).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.6 (q, *C*H$_3$C=), 21.5 (q, *C*H$_3$CH), 23.6 (d, *C*HCH$_2$), 23.7 (q, *C*H$_3$CH), 39.2 (t, *C*H$_2$CH), 75.6 (d, OCH), 88.0 (d, OOCH), 104.0 (d, OCHOO), 118.7 (t, CH_2=), 124.0 (d, CH_{arom}), 126.1 (d, CH_{arom}), 126.6 (d, CH_{arom}), 126.7 (d, CH_{arom}), 127.6 (d, CH_{arom}), 128.0 (d, CH_{arom}), 128.3 (d, CH_{arom}), 131.9 (s, C_{arom}), 132.8 (s, C_{arom}), 133.9 (s, C_{arom}), 138.6 (s, *C*=CH$_2$).

MS (EI, 70 eV): *m*/*z* (%) = 312 (M^+, 3), 226 ($M^+ - C_5H_{10}O$, 2), 156 ($C_{11}H_8O^+$, 100), 155 ($C_{11}H_7O^+$, 100), 128 ($C_{10}H_8^+$, 30), 127 ($C_{10}H_7^+$, 100), 124 ($C_9H_{16}^+$, 27), 109 ($C_8H_{13}^+$, 17).

HRMS (EI, 70 eV): $C_{20}H_{24}O_3$ calcd: M = 312.173 g/mol; found: M = 312.173 ± 0.005 g/mol.

Anal. Calcd for $C_{20}H_{24}O_3$ (312.40): C, 76.89; H, 7.74. Found: C, 76.61; H, 7.63

(5*RS*,6*RS*)-5-Methyl-6-(prop-1-en-2yl)spiro[1,2,4-trioxacyclohexane-3,2′-adamantane] (30c) (Method A)

A solution of **14** (2.0 g, 15.2 mmol) and adamantanone (2.28 g, 15.2 mmol) in CH_2Cl_2 were treated with catalytic amounts of $BF_3{\cdot}OEt_2$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EtOAc–*n*-hexane, 1:10, R_f 0.89) afforded the pure 1,2,4-trioxane **30c** as a colorless oil which crystallized on standing (0.47 g, 12%); mp 48–49 °C.

IR (film): 2912, 1648, 1222, 1109, 1090, 1023, 999, 926 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (d, 3 H, *J* = 6.2 Hz, C*H*$_3$CH), 1.52–2.11 (m, 13 H, CH and CH_2), 1.73 (m, 3 H, CH_3C=), 2.90 (br d, 1 H, CH), 4.04 (dq, 1 H, *J* = 6.2, 9.6 Hz, OCH), 4.17 (d, 1 H, *J* = 9.6 Hz, OOCH), 5.04 (m, 2 H, CH_2=).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.0 (q, *C*H$_3$CH), 19.8 (q, *C*H$_3$C=), 27.1 (d, CH), 27.2 (d, CH), 29.8 (d, CH), 36.5 (d, CH), 33.1 (t, CH_2), 33.3 (t, CH_2), 33.4 (t, CH_2), 33.5 (t, CH_2), 37.2 (t, CH_2), 65.0 (d, OCH), 88.7 (d, OOCH), 104.8 (s, OCOO), 117.6 (t, CH_2=), 139.3 (s, *C*=CH$_2$).

MS (EI, 70 eV): *m*/*z* (%) = 264 (M^+, 4), 220 ($M^+ - C_2H_4O$, 55), 150 ($C_{10}H_{14}O^+$, 34), 82 ($C_6H_{10}^+$, 100), 81 ($C_6H_9^+$, 53), 80 ($C_6H_8^+$, 82), 79 ($C_6H_7^+$, 97), 67 ($C_5H_7^+$, 67), 55 ($C_3H_3O^+$, 42).

Anal. Calcd for $C_{16}H_{24}O_3$ (264.36): C, 72.69; H, 9.15. Found: C, 72.69; H, 9.05.

(5*RS*,6*RS*)-5-Isobutyl-6-(prop-1-en-2yl)spiro[1,2,4-trioxacyclohexane-3,2′-adamantane] (30d) (Method A)

A solution of **25** (R = *i*-Bu) (1.70 g, 9.77 mmol) and adamantanone (2.10 g, 13.5 mmol) in CH_2Cl_2 was treated with catalytic amounts of $BF_3{\cdot}OEt_2$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EtOAc–*n*-hexane, 1:10, R_f 0.80) afforded the 1,2,4-trioxane **30d** (0.28 g, 10%) as an oil which crystallized on standing to a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, 3 H, *J* = 6.6 Hz, C*H*$_3$CH), 0.90 (d, 3 H, *J* = 6.8 Hz, C*H*$_3$CH), 1.01–1.10 (m, 1 H, C*H*$_2$CH), 1.34 (m, 1 H, C*H*$_2$CH), 1.50–2.09 [m, 14 H, CH, CH_2 and C*H*(CH$_3$)$_2$], 1.72 (t, 3 H, *J* = 1.2 Hz, C*H*$_3$C=), 2.91 (br d, 1 H, CH), 3.99 (ddd, 1 H, *J* = 3.0, 9.5, 9.5 Hz, OCH), 4.20 (d, 1 H, *J* = 9.5 Hz, OOCH), 5.03 (m, 2 H, CH_2=C).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 19.7 (q, *C*H$_3$C=), 21.4 (q, *C*H$_3$CH), 23.5 (d, *C*HCH$_2$), 23.8 (q, *C*H$_3$CH), 27.2 (2 d, CH), 29.9 (d, CH), 33.1 (t, CH_2), 33.3 (2 t, CH_2), 33.5 (t, CH_2), 36.6 (d, CH), 37.2 (t, CH_2), 39.9 (t, *C*H$_2$CH), 66.6 (d, OCH), 87.8 (d, OOCH), 104.7 (s, OCOO), 118.0 (t, *C*H$_2$=C), 139.3 (s, *C*=CH$_2$).

MS (EI, 20 eV): *m*/*z* (%) = 150 ($C_{10}H_{14}O^+$, 100), 124 ($C_9H_{16}^+$, 27).

HRMS (EI, 70 eV): $C_{19}H_{30}O_3$ calcd: M = 306.2195 g/mol; found: M = 306.219 ± 0.005 g/mol.

Anal. Calcd for $C_{19}H_{30}O_3$ (306.44): C, 74.47; H, 9.87. Found: C, 74.06; H, 9.78.

(3*RS*,5*RS*,6*RS*)-3-(Furan-2-yl)-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane (30e) (Method A)

A solution of **14** (0.71 g, 5.38 mmol) and furan-2-carboxaldehyde (0.65 g, 6.77 mmol) in CH_2Cl_2 was treated with catalytic amounts of $BF_3{\cdot}OEt_2$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EtOAc–*n*-hexane, 1:10) afforded the pure 1,2,4-trioxane **30e** as a viscous colorless oil (0.38 g, 34%).

IR (film): 3126, 3085, 2979, 2901, 1647, 1636, 1601, 1149, 1087, 1065, 1000, 984, 915 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (d, 3 H, *J* = 6.3 Hz, C*H*$_3$CH), 1.74 (m, 3 H, CH_3C=), 4.0 (dq, 1 H, *J* = 6.3, 9.1 Hz, OCH), 4.45 (d, 1 H, *J* = 9.1 Hz, OOCH), 5.09 (m, 2 H, CH_2=), 6.25 (s, 1 H, OCHOO), 6.34 (m, 1 H, CH), 6.53 (m, 1 H, CH), 7.39 (m, 1 H, CH).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.2 (q, *C*H$_3$CH), 19.5 (q, *C*H$_3$C=), 74.1 (d, OCH), 88.7 (d, OOCH), 98.4 (d, OCHOO), 110.0 (d, CH=), 110.3 (d, CH=), 118.4 (t, *C*H$_2$=C), 138.4 (s, *C*=CH$_2$), 143.3 (d, OCH=), 147.3 (s, OC_q=).

Anal. Calcd for $C_{11}H_{14}O_4$ (210.23): C, 62.85; H, 6.71. Found: C, 62.80; H, 6.70.

Table 1 Crystal Data for Compounds **23a**, **26d** and *tat*-**29a**

Product	Formula M [gmol^{-1}]	Cell Dimensions [Å]	α, β, γ [°]	V [Å^3], Z	Crystal System Space Group	Reflexes Measd/ Reflexes Obsvd	R/R$_W$
23a	$C_{18}H_{26}O_3$	a = 7.388(1) b = 10.428(1) c = 20.250(1)	α = 90 β = 94.19 γ = 90	V = 1555.9(3) Z = 4	monoclinic P21/n	9215 1805	0.0586 0.1128
26d	$C_{19}H_{20}O_3$	a = 12.8550(6) b = 14.8204(5) c = 8.3185(3)	α = 90 β = 94.95 γ = 90	V = 1578.90(11) Z = 4	monoclinic P21/c	3443 1851	0.0507 0.1112
***tat*-29a**	$C_{24}H_{36}O_6$	a = 23.634(1) b = 8.201(1) c = 11.220(1)	α = 90 β = 90 γ = 90	V = 2174.7(3) Z = 4	orthorhombic Pbcn	1441 321	0.0773 0.0682

(3*RS*,5*RS*,6*RS*)-3-(2-Chlorophenyl)-5-ethyl-6-(prop-1-en-2-yl)-1,2,4-trioxane (30f) (Method A)

A solution of **25** (R = Et) (1.50 g, 10.3 mmol) and 2-chlorobenzaldehyde (1.44 g, 10.2 mmol) in CH_2Cl_2 was treated with catalytic amounts of $BF_3{\cdot}OEt_2$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EtOAc–*n*-hexane, 1:10) afforded the 1,2,4-trioxane **30f** (0.60 g, 22%) as an oil.

IR (film): 3079, 2971, 2925, 2879, 1647, 1597, 1576, 1445, 1086, 1053, 1003, 960, 916 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (dd, 3 H, *J* = 7.4, 7.4 Hz, C*H*$_3$CH$_2$), 1.43–1.62 (m, 2 H, C*H*$_2$CH$_3$), 1.73 (m, 3 H, CH$_3$C=), 3.82 (ddd, 1 H, *J* = 3.5, 8.1, 9.2 Hz, OCH), 4.48 (d, 1 H, *J* = 9.2 Hz, OOCH), 5.05 (m, 2 H, CH$_2$=), 5.48 (s, 1 H, OCHOO), 7.21–7.65 (m, 4 H$_{arom}$).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.3 (q, *C*H$_3$CH$_2$), 19.7 (q, *C*H$_3$C=), 23.6 (t, *C*H$_2$CH$_3$), 78.7 (d, OCH), 87.4 (d, OOCH), 101.0 (d, OCHOO), 118.5 (t, *C*H$_2$=C), 126.8 (d, CH$_{arom}$), 128.7 (d, CH$_{arom}$), 129.5 (d, CH$_{arom}$), 130.9 (d, CH$_{arom}$), 132.1 (s, C$_{arom}$), 133.5 (s, C$_{arom}$), 138.7 (s, *C*=CH$_2$).

MS (EI, 70 eV): *m*/*z* (%) = 142 ($C_7H_5{}^{37}Cl^+$, 13), 141 ($C_7H_4{}^{37}Cl^+$, 42), 140 ($C_7H_5{}^{35}Cl^+$, 39), 139 ($C_7H_4{}^{35}Cl^+$, 100), 113 ($C_6H_5{}^{37}Cl^+$, 7), 111 ($C_6H_5{}^{35}Cl^+$, 21), 96 ($C_7H_{12}{}^+$, 30), 81 ($C_6H_9{}^+$, 20).

Anal. Calcd for $C_{14}H_{17}ClO_3$ (268.74): C, 62.57; H, 6.38. Found: C, 62.55; H, 6.36.

(3*RS*,5*RS*,6*RS*)-3-Ethoxy-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane and (3*RS*,5*SR*,6*SR*)-3-Ethoxy-5-methyl-6-(prop-1-en-2-yl)-1,2,4-trioxane (30g) (Method B)

A solution of **14** (0.75 g, 5.68 mmol) and triethyl orthoformate (5.0 g, 33.8 mmol) in CH_2Cl_2 was treated with catalytic amounts of $BF_3{\cdot}OEt_2$ (0.2 mL). Usual work-up followed by evaporation of excess orthoester afforded an oil composed of a diastereomeric mixture of the 1,2,4-trioxanes **30g** in the ratio of 72:28 (0.75 g, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (major diastereomer) = 1.19 (d, 3 H, *J* = 6.3 Hz, C*H*$_3$CH), 1.24 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$CH$_2$), 1.72 (t, 3 H, *J* = 1.3 Hz, CH$_3$C=), 3.83 (m, 2 H, C*H*$_2$CH$_3$), 4.02 (dq, 1 H, *J* = 9.2, 6.3 Hz, OCH), 4.20 (d, 1 H, *J* = 9.2 Hz, OOCH), 5.07 (m, 2 H, CH$_2$=C), 5.77 (s, 1 H, OCHOO).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ (major diastereomer) = 15.2 (q, *C*H$_3$CH$_2$), 16.2 (q, *C*H$_3$CH), 19.6 (q, *C*H$_3$C=), 63.8 (d, OCH), 74.3 (t, *C*H$_2$CH$_3$), 87.5 (d, OOCH), 113.3 (d, OCHOO), 118.5 (t, *C*H$_2$=C), 137.8 (s, *C*=CH$_2$).

^{1}H NMR (300 MHz, $CDCl_3$): δ (additional significant signals of the minor diastereomer) = 1.74 (t, 3 H, *J* = 1.1 Hz, CH$_3$C=), 3.60 (dq, 1 H, *J* = 9.7, 7.1 Hz, OCH), 3.71 (m, 2 H, C*H*$_2$CH$_3$), 5.58 (s, 1 H, OCHOO).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ (minor diastereomer) = 14.7 (q, *C*H$_3$CH$_2$), 16.1 (q, *C*H$_3$CH), 19.5 (q, *C*H$_3$C=), 61.6 (t, *C*H$_2$CH$_3$), 65.8 (d, OCH), 88.9 (d, OOCH), 110.0 (d, OCHOO), 118.2 (t, *C*H$_2$=C), 139.0 (s, *C*=CH$_2$).

MS (EI, 70 eV): *m*/*z* (%) = 82 ($C_6H_{10}{}^+$, 100), 70 ($C_4H_6O^+$, 28), 69 ($C_4H_5O^+$, 27), 67 ($C_5H_7{}^+$, 68).

Crystallographic Data (Table 1)

Data Collection: Nonius-Kappa-CCD diffractometer, room temperature, Mo-K$_\alpha$-radiation (λ = 0.71073 Å), graphite monochromator, φ – ω – scans, 2 Θ limits [°]: 2–54.

Structure Analysis and Refinement: Solved by direct methods; full matrix least-squares refinement with anisotropic thermal parameters for C, N and O and isotropic parameters for H.

Programs Used: For structure determination SHELXS-97 and for refinement SHELXL-97.

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